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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/315,292	05/20/99	BENNETT	ID15-3561

HM12/0524

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ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 05/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

U.S. G.P.O. 1999 460-693

Office Action Summary	Application No. 09/315,292	Applicant(s) BENNETT ET AL.
	Examiner Mark L. Shibuya	Group Art Unit 1635

X Responsive to communication(s) filed on *Mar 23, 2000*.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-63* is/are pending in the application.

Of the above, claim(s) *1-36 and 62* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *37-53, 58, and 63* is/are rejected.

X Claim(s) *54-57 and 59-61* is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

X See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

X The specification is objected to by the Examiner.

X The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *4,7*

Interview Summary, PTO-413

X Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group II, claims 37-61 and 63, phophorothioate linkages and the gene ICAM-1 (designated species "B2") in Paper No. 6, filed 3/30/00, is acknowledged. The traversal is on the ground(s) that the Restriction requirement in the Office action mailed 1/18/00 failed to indicate any burden that would [be] encountered by the examiner if Groups I and II were maintained in the present patent application. Furthermore, a search of the claims of Group I would only encompass a single class and subclass.

a. These arguments are not found persuasive because the Restriction requirement in the Office action, mailed 1/18/00, stated that the inventions are related as product and process of use, but are distinct because the product may be used in a materially different process, and because the inventions have acquired a separated status in the art because of their recognized divergent subject matter. Furthermore, applicants' argument to the fact that invention of Group I is properly classifiable in a separate class and subclass is, in itself, a ground for requiring restriction.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

2. The information disclosure statement filed 9/15/99 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be

listed. It has been placed in the application file, and the information referred to therein has been considered, except as noted immediately below.

a. The following applicant references have no been considered because no copies have been furnished thereof: AA, CW, DN, EJ , GI, GM, HK, HM-HO, and ID. Applicant reference CE, Martin et al., which is written in German, has been considered only to the extent of reference CE's English abstract.

b. The following U.S. Application Serial Numbers have been considered: Reference LF, 08/383,666; LH, 08/465,880; LI, 08/468,037; LL, 09/009,490; LN, 09/044,506; LP, 09/071,433. Although these applications have been considered, reference to them on the PTO-1449 has been removed as failing to comply with 37 CFR 1.98 because they do not have publication dates. The following U.S. Application Serial Numbers were not available to the examiner and have not been considered: Reference LG 08/398,901; LJ, 08/762,488; LK, 08/777,266; LM, 09/016,520; LO, 09/062,416. These application will be considered as they become available to the examiner. Reference LJ, 08/762,488 appears to have been cited in error by applicant, because the application is from an non analogous field of art.

c. Reference AC is objected to because AC cites to "http://ww.paddocklabs.com/secundum/secarndx.html". Embedded hyperlinks and/or other forms of browser-executable code are impermissible and must be deleted. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP

608.01(p), paragraph I regarding incorporation by reference. Furthermore if the application should issue and be placed on the Office web page, the URL may be interpreted as a valid HTML code and become a live web link, transferring an user to a commercial web site (in the instant case, Secundum Artem). Office policy does not permit the Office to link to any commercial site because the Office exercises no control over the organization, views or accuracy of the information contained on these outside sites. The rules for citing electronic documents as prior art are now available in the paper version of the MPEP, 7th edition, revision 1 dated Feb. 2000 at 707.05(e).

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or **non-dated** alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

4. The specification is objected to because the reference on page 22, lines 29-32, to U.S. Patent application 08/762,488, filed on December 10, 1996, appears to be incorrect because said application is not commonly owned with the instant application as described and appears to be of a non analogous art.

5. The specification at p. 46, lines 25-30, is objected to for reciting "http://ww.paddocklabs.com/secundum/secarndx.html". Embedded hyperlinks and/or other forms of browser-executable code are impermissible and must be deleted. See MPEP 608.01(p), paragraph I regarding incorporation by reference. The rules for citing electronic documents as prior art are now available in the paper version of the MPEP, 7th edition, revision 1 dated Feb. 2000 at 707.05(e). *See, also*, above objection to the Information Disclosure Statement, at paragraph 2.c. of the instant Office action.

Claim Objections

6. Claims 54-57 and 59-61 are objected to as being dependent upon base claim 1 that is non-elected, but would not be objected to if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Double Patenting

7. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

8. Applicant is advised that should claim 59 be found allowable, claim 60 will be objected to under 37 CFR 1.75 as being a duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

9. Claims 37-61 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 37-61 of copending Application No. 09/083,586. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 37, 42, and 44-61 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-46 and 50-53 of copending Application No. 09/083,585. Although the conflicting claims are not identical, they are

not patentably distinct from each other because the methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide wherein the sugar moiety of at least one nucleoside unit of said oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or wherein at least one internucleotide linkage within said oligonucleotide is *not a phosphodiester or* wherein at least one internucleotide linkage within said oligonucleotide is *not a phosphorothioate* linkage and variations thereof; wherein at least one internucleotide linkage is 3'-methylenephosphonate, a non-phosphorus containing oligonucleoside linkage, a 2'-5' linkage or a 3'-deoxy-3'-aminophosphoramide linkage, methods of treating an animal having or suspected of having a disease or disorder that is treatable with one or more nucleic acids comprising administering an aerosolized nucleic acid composition to the lungs of the animal; methods of investigating the role of a gene or gen product in an animal other than a human comprising administering the aerosolized nucleic acid composition; and a medical device for pulmonary delivery of an aerosol of the instant invention, **would encompass** methods comprising oligonucleotides with phosphorothioate linkages that are not phosphodiester *or* oligonucleotides with phosphodiester linkages that are not phosphorothioate, which would have been obvious over the methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide and variations thereof; methods of treating an animal having or suspected of having a disease or disorder that is treatable

with one or more nucleic acids comprising administering an aerosolized nucleic acid composition to the lungs of the animal; methods of investigating the role of a gene or gene product in an animal other than a human comprising administering the aerosolized nucleic acid composition; and a medical device for pulmonary delivery of an aerosol, of copending Application No. 09/083,585.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 37, 42, and 44-61 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-46 and 50-53 of copending Application No. 09/315,581. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide wherein the sugar moiety of at least one nucleoside unit of said oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or wherein at least one internucleotide linkage within said oligonucleotide is *not a phosphodiester or* wherein at least one internucleotide linkage within said oligonucleotide is *not a phosphorothioate* linkage and variations thereof; wherein at least one internucleotide linkage is 3'-methylenephosphonate, a non-phosphorus containing oligonucleoside linkage, a 2'-5' linkage or a 3'-deoxy-3'-aminophosphoramide linkage, methods of treating an animal having or suspected of having a disease or disorder that is treatable with one or more

nucleic acids comprising administering an aerosolized nucleic acid composition to the lungs of the animal; methods of investigating the role of a gene or gene product in an animal other than a human comprising administering the aerosolized nucleic acid composition; and a medical device for pulmonary delivery of an aerosol of the instant invention, **would encompass** methods comprising oligonucleotides with phosphorothioate linkages that are not phosphodiester *or* oligonucleotides with phosphodiester linkages that are not phosphorothioate, which would have been obvious over the methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide and variations thereof; methods of treating an animal having or suspected of having a disease or disorder that is treatable with one or more nucleic acids comprising administering an aerosolized nucleic acid composition to the lungs of the animal; methods of investigating the role of a gene or gen product in an animal other than a human comprising administering the aerosolized nucleic acid composition; and a medical device for pulmonary delivery of an aerosol, of copending Application No. 09/315,581.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 U.S.C. § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 37-51, 53, 58, 61 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Independent claim 37, and its dependent claims, recite the term "an nucleic acid" in lines 1 and 2 and should instead recite "a nucleic acid".

b. Claim 37 recites the limitation "the nucleic acid composition" in line 6 and "the aerosolized nucleic acid composition" in lines 7 and 9. There are no antecedent bases for these limitations in the claim.

c. Claim 49 recites the language "contains more than one oligonucleotide", which renders the claim vague and indefinite, because it is not clear if the claimed invention contains more than one oligonucleotide species or type or sequence, etc., of oligonucleotide, or merely more than one oligonucleotide molecule.

d. Claims 51 and 58 recites the language "is aerosolized solution consists essentially of", which does not make sense. Correction is required, possibly by replacing with the language --is an aerosolized solution that consists essentially of--.

e. Claim 53 in line 1 recites the language "the role of gene". Correction is required, possibly by replacing with the language --the role of a gene--.

f. Claim 61 misspells "with" as "ith". Correction is necessary.

g. The term "ISIS-15839" in claim 63 renders the claim vague and indefinite because the term is not defined by the claim, and the specification does not provide a definition for the term,

so that one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. *See, also* below rejection under 35 U.S.C. 112, Paragraph 1, Written Description and Enablement.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claim 63 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for lack of Written Description.

a. Claim 63 is drawn to the method of claim 37, wherein said oligonucleotide is ISIS-15839.

b. The specification discloses the following oligonucleotides: ISIS 2503 (Specification at p. 8, line 30 and Figure 2), ISIS-2105, ISIS-17009, ISIS-15163, ISIS-2205, and ISIS-17709 (Specification at p. 58, line 32-67, line 16).

c. No other oligonucleotides designated by an "ISIS" designation are taught by the specification as filed other than those recited above. The specification as filed fails to provide any written description at all for ISIS-15839, or what sequences and molecular modifications is required for the invention as claimed. Therefore the specification as filed fails to provide any

written description for ISIS-15839 and fails to provide any guidance on how the other ISIS oligonucleotides taught would have lead one to be in possession of ISIS-15839. Thus, applicants disclosure is not sufficient to describe the claimed ISIS-15839 oligonucleotide, in such clear and concise and exact terms as to show applicants were in possession of the claimed invention.

17. Claim 63 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The nucleotide sequence and any oligonucleotide modifications for the oligonucleotide ISIS-15839, which are critical or essential to the practice of the invention, but not included in the claim(s), is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The specification at, *e.g.*, p. 4, line 37-p. 5, line 3, contemplates the oligonucleotides used in the claimed methods of disease treatment as antisense oligonucleotides, *i.e.*, the oligonucleotide binds to the complementary portion of a target nucleic acid. The specification at, *e.g.*, p. 18, lines 21-34, contemplate oligonucleotide modifications for increased stability. These features for ISIS-15839 are considered essential by the applicant for the claimed methods of treatment, but are not taught by the specification as filed, or reflected in claim 63.

Claim Rejections - 35 U.S.C. § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

19. Claims 37, 42-48, and 50-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Nyce, WO 96/40266.

a. Nyce, WO 96/40266, at p. 7, lines 22-37, p. 8, lines 11-18, p. 9, lines 14-16, p. 10, lines 13-23, p. 11, lines 1-20, p. 12, line 1-p. 13, line 27, p. 17, line 32-p. 18, line 2, and p. 19, lines 16-21, disclose methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide, wherein at least one internucleotide linkage within said oligonucleotide is not a phosphodiester and wherein at least one internucleotide linkage within said oligonucleotide is not a phosphorothioate linkage; wherein at least one internucleotide linkage is a non-phosphorus containing oligonucleoside linkage, wherein the composition comprises sterilized, pyrogen free water and saline solution, wherein the composition is a powder, wherein the oligonucleotide is an antisense oligonucleotide in saline solution; methods of treating an animal having or suspected of having a disease or disorder that is treatable with one or more nucleic acids comprising administering an aerosolized nucleic acid composition to the lungs of the animal and wherein the disease is asthma; methods of investigating the role of a gene or gen product in an animal other than a human comprising administering the

aerosolized nucleic acid composition; and a medical device that is a nebulizer for pulmonary delivery of an aerosol.

20. Claims 37, 42, 44-48, and 50-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Debs et al., U.S. Patent No. 5,641,662 (applicant's reference AA, IDS filed 4/3/00).

a. Debs et al., U.S. Patent No. 5,641,662, at col. 1, lines 12-16, col. 4, lines 24-45, col. 10, lines 19-22, 27-29, 36-41, col. 18, lines 49-57, col. 20, lines 5-19 and 43-65, col. 22, lines 10-11, 22-23, 55-56, col. 23, lines 22-27, col. 24, lines 23-32, col. 28, lines 26-40, and col. 30, lines 20-31, disclose methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide, wherein at least one internucleotide linkage within said oligonucleotide is not a phosphorothioate linkage, wherein the composition comprises sterilized, pyrogen free water and saline solution, wherein the composition is a powder, wherein the oligonucleotide is an antisense oligonucleotide in saline solution; methods of treating an animal having or suspected of having a disease or disorder that is treatable with one or more nucleic acids comprising administering an aerosolized nucleic acid composition to the lungs of the animal and wherein the disease comprises lung cancer, asthma, bronchitis, pneumonia and cystic fibrosis; methods of investigating the role of a gene or gene product in an

animal other than a human comprising administering the aerosolized nucleic acid composition; and a medical device that is a nebulizer for pulmonary delivery of an aerosol.

Claim Rejections - 35 U.S.C. § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 37-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Nyce or Debs et al., as applied to claim 37 above, and each further in view of Milligan et al., Baker et al., U.S. Patent No. 5,789,573, Bennett et al., U.S. No. 5,955,443, and Ravikumar et al. U.S. No. 5,554,746.

a. **Nyce, WO 96/40266**, at p. 7, lines 22-37, p. 8, lines 11-18, p. 9, lines 14-16, p. 10, lines 13-23, p. 11, lines 1-20, p. 12, line 1-p. 13, line 27, p. 17, line 32-p. 18, line 2, and p. 19, lines 16-21, teach methods of administration of a nucleic acid therapeutic or diagnostic

composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal and wherein the oligonucleotide has at least one phosphodiester linkage.

b. **Debs et al., U.S. Patent No. 5,641,662**, at col. 1, lines 12-16, col. 4, lines 24-45, col. 10, lines 19-22, 27-29, 36-41, col. 18, lines 49-57, col. 20, lines 5-19 and 43-65, col. 22, lines 10-11, 22-23, 55-56, col. 23, lines 22-27, col. 24, lines 23-32, col. 28, lines 26-40, and col. 30, lines 20-31, disclose teach methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal and wherein the oligonucleotide has at least one phosphodiester linkage.

c. Neither of Nyce or Debs et al. teach oligonucleotides, wherein the sugar moiety of at least one nucleoside unit of the oligonucleotides is not a 2'-deoxyribofuranosyl sugar moiety or wherein the oligonucleotide comprises at least one nucleoside unit that is a 2'-O-substituted nucleoside unit, a 2'-O-alkoxyalkoxy substituent or a 2'-O-diakylaminooxyalkyl substituent, and wherein at least one internucleotide linkage is 3'-methylenephosphonate.

d. **Milligan et al.**, at p. 1932, para 7-p. 1933, para 1, teach oligonucleotides wherein the sugar moiety of at least one nucleoside unit of said oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety and wherein the oligonucleotide comprise a 2'-O-substituted nucleoside unit, in order to enhance resistance to degradation.

e. **Baker et al., U.S. Patent No. 5,789,573**, at col. 3, lines 45-50, col. 4, lines 26-28, teach oligonucleotides that comprise a 2'-alkoxyalkoxy substituents in order to enhance the

affinity of an antisense oligonucleotide for its target nucleic acid and more resistant to *in vitro* and *in vivo* degradation. teach oligonucleotides that comprise a 2'-O-alkoxyalkoxy substituent.

f. **Bennett et al., U.S. No. 5,955,443**, at col. 3, lines 15-18, col. 11, lines 36-65, teach oligonucleotides that comprise a 2'-O-diakylaminooxyalkyl substituent that is 2'-dimethylaminooxyethoxy in order to enhance the affinity of an antisense oligonucleotide for its target nucleic acid and more resistant to *in vitro* and *in vivo* degradation.

g. **Ravikumar et al. U.S. No. 5,554,746**, at col. 2, lines 27-33 and 36-37, teach oligonucleotides that comprise at least one internucleotide linkage is 3'-methylenephosphonate in order to improve half life as well as membrane penetration.

h. It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the sugar moiety of at least one nucleoside unit of said oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety, wherein the composition comprises at least one oligonucleotide wherein at least one nucleoside unit is a phosphodiester, 2'-O-substituted nucleoside unit, a 2'-O-alkoxyalkoxy substituent or a 2'-O-diakylaminooxyalkyl substituent, and wherein at least one internucleotide linkage is 3'-methylenephosphonate.

i. One of ordinary skill in the art would have been motivated to have used methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the sugar

moiety of at least one nucleoside unit of said oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety, wherein the composition comprises at least one oligonucleotide wherein at least one nucleoside unit is a 2'-O-substituted nucleoside unit, a 2'-O-alkoxyalkoxy substituent or a 2'-O-diakylaminooxyalkyl substituent, and wherein at least one internucleotide linkage is 3'-methylenephosphonate, in order to enhance stability and cellular uptake of the oligonucleotide, as taught by the aforementioned prior art.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mark L. Shibuya (SRC), Ph.D.*, whose telephone number is (703) 308-9355.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

25. Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is (703) 308-0196.

Mark L. Shibuya
Patent Examiner
Technical Center 1600
May 22, 2000